

Letter to the Editor

Octreot

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Octreotide, a Long-Acting Somatostatin Analogue, in Diabetic Neuropathic Pain

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Dear Sir,

Somatostatin is an effective analgesic when given intravenously in patients with cluster headache [1], or injected intrathecally in post-operative [2] and cancer pain [3]. The analgesic effect of somatostatin is unexplained, but it may act centrally to block the transmission of painful impulses by inhibiting substance P release in the substantia gelatinosa of the dorsal horn of the spinal cord [4, 5]. Somatostatin analogues, which are better suited to clinical use than the native peptide, also have analgesic properties. For example, subcutaneous injections of octreotide (Sandostatin, or SMS 201-995; Sandoz), a long-acting somatostatin analogue, produced a dramatic and sudden improvement in intractable headache in patients with acromegaly or prolactinoma [6-8].

The analgesic properties of a somatostatin analogue (octreotide) were studied in 6 diabetic patients with chronic painful peripheral neuropathy which had failed to respond to conventional treatments. The 6 diabetic patients comprised 5 males and 1 female, aged 52-66 years (mean 59.8 ± 2.0 SEM). The median duration of diabetes was 14.0 years (range 2-18 years) and median duration of pain was 5 years (range 2-8 years). Five patients were insulin treated (range of dosage 0.47-0.62 U/kg/day), and 2 were clinically judged to be truly insulin dependent; the other was taking metformin. The mean glycosylated haemoglobin was $10.1 \pm 0.5\%$ (range 8.8-12.2%; normal <8%). Previous treatments had included: tricyclic antidepressants ($n = 6$), dihydrocodeine ($n = 1$), mexiletine ($n = 2$), and sodium valproate ($n = 1$); none had produced consistent symptomatic relief.

All patients were studied for 3 consecutive days. After a run-in day (no injections), the 6 patients were randomly allocated in a double-blind fashion to receive one

dose of 100 µg (1 ml) of octreotide, or an equal volume of placebo (octreotide diluent; sodium acetate-acetic acid buffer, pH 4.0). All injections were administered subcutaneously in the abdomen at 2 p.m. by A.W.C. On each of the 3 consecutive study days, visual analogue pain scores (VAS) were measured at 15- to 30-min intervals (from 1.30 to 4 p.m.) and then at 4, 5, 6, 8, and 19 p.m. The VAS was recorded by the patient on an unmarked 10-cm horizontal line ranging from 'no pain' to 'worst pain ever'. An indwelling intravenous catheter in the forearm was kept patent with heparinised saline to permit venous blood sampling for measurement of glucose concentration at intervals of 15-30 min from 1.30 to 4 p.m. and finally at 6 p.m. During the 3 days, the 6 patients were kept on all current medications, including their usual dose of analgesics. Informed written consent was obtained from all patients, and the study was approved by the hospital ethical committee.

Differences in mean VAS on the 3 consecutive days (run-in and octreotide or placebo injection) were compared using analysis of variance followed by Student's paired t tests. Data are shown throughout as mean \pm SEM. The mean baseline blood glucose concentration on the 3 days did not differ significantly: run-in, 12.2 ± 1.3 mmol/l; octreotide, 16.1 ± 1.3 mmol/l; placebo, 15.0 ± 1.6 mmol/l. On each study day, there was also no significant change in mean blood glucose concentration following placebo or octreotide. The mean VAS on the 3 days did not differ significantly: run-in, 5.3 ± 0.9 cm; octreotide, 5.8 ± 1.2 cm; placebo, 5.9 ± 1.0 cm. On each study day, there was no significant change in VAS following placebo or octreotide.

In conclusion, the present study showed that 100 µg of the long-acting somatostatin analogue (octreotide) administered subcutaneously once daily had no effect on

the severity of diabetic neuropathic pain. The time scale of this study was based on the assumption that pain relief with octreotide may occur rapidly following subcutaneous injections. For example, Williams et al. [6, 8] reported that the analgesic effect of subcutaneous octreotide on headaches associated with pituitary tumours may occur within 2–10 min after injection and last for up to 6 h. Most previous studies administered somatostatin to patients with nociceptive (i.e. tissue damage) pain of short duration [1, 2]. The diabetic patients reported in this study have had chronic neuropathic pain with a median duration of symptoms of 5 years; this predominantly neurogenic pain may be unresponsive to somatostatin, for reasons that are currently unknown. It remains to be seen whether octreotide is effective in recent-onset diabetic neuropathic pain.

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References

- 1 Sicuteli F, Geppetti P, Marabini S, Lembeck F: Pain relief by somatostatin in attacks of cluster headache. *Pain* 1984;18:359–365.
- 2 Chribasik J, Meynadier J, Scherpereel P, Wunsch E: The effects of epidural somatostatin on postoperative pain. *Anesth Analg* 1985;65:1085–1088.
- 3 Meynadier J, Chribasik J, Dubar M, Wunsch E: Intrathecal somatostatin in terminally ill patients: A report of two cases. *Pain* 1985;23:9–12.
- 4 Hökfelt T, Kellerth JA, Nilsson G, Pernow B: Experimental immunohistochemical studies on the localization and distribution of substance P in cat primary sensory neurones. *Brain Res* 1975;100:235–252.
- 5 Randic M, Miletic V: Depressant actions of methionine-enkephalin and somatostatin in cat dorsal horn neurones activated by noxious stimuli. *Brain Res* 1978;152:196–202.
- 6 Sandler LM, Burrin JM, Williams G, Joplin GF, Carr DH, Bloom SR: Effective long-term treatment of acromegaly with long-acting somatostatin analogue (SMS 201-995). *Clin Endocrinol* 1987;26:85–95.
- 7 Williams G, Ball JA, Joplin GF, Bloom SR: Improvement in headache associated with prolactinoma during treatment with the somatostatin analog, SMS 201-995. An 'n of 1' study. *N Engl J Med* 1986;315:1166–1167.
- 8 Williams G, Ball JA, Lawson RA, Maskill MR, Joplin GF, Bloom SR: Analgesic effect of somatostatin analogue (octreotide) in headache associated with pituitary tumours. *Br Med J* 1987;295:247–248.

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